



Antibiotics, Gastrointestinal Therapeutic Class Review (TCR)

February 1, 2016

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
fidaxomicin (Dificid®) ¹	Optimer Pharm	Treatment of <i>Clostridium difficile</i> -associated diarrhea (CDAD) in adults 18 years and older
metronidazole (Flagyl®) ²	generic	Trichomoniasis Amebiasis (acute intestinal amebiasis and amebic liver abscess) Anaerobic bacterial infections – Oral therapy may be used following intravenous metronidazole therapy in serious infections caused by <i>Bacteroides</i> species including intra-abdominal infections, skin and skin structure infections, gynecologic infections, bacterial septicemia, bone and joint infections (as adjunctive therapy), central nervous system infections, lower respiratory tract infections, and endocarditis
metronidazole extended-release (ER) (Flagyl® ER) ³	Pfizer	Bacterial vaginosis in non-pregnant women
neomycin ⁴ (Neo-Fradin)	generic	Suppression of bowel flora – Pre-operative bowel preparation as single therapy or in combination with erythromycin Adjunctive therapy for treatment of hepatic encephalopathy
nitazoxanide (Alinia®) ^{5*}	Romark Pharm	Diarrhea caused by <i>Giardia lamblia</i> <ul style="list-style-type: none"> Oral tablet is indicated for patients ≥ 12 years old Oral suspension is indicated for patients > 1 year old Diarrhea caused by <i>Cryptosporidium parvum</i> <ul style="list-style-type: none"> Oral suspension is indicated for patients 1 to 11 years of age
paromomycin ⁶	generic	Amebiasis (acute and chronic intestinal) Management of hepatic encephalopathy as adjunctive therapy
rifaximin (Xifaxan®) ⁷	Salix	Treatment of traveler's diarrhea caused by noninvasive strains of <i>Escherichia coli</i> (patients ≥ 12 years of age). Rifaximin should not be used in patients with diarrhea complicated by fever or blood in stool or diarrhea due to pathogens other than <i>E. coli</i> Reduction in the risk of overt hepatic encephalopathy recurrence in patients ≥ 18 years of age Treatment of irritable bowel syndrome (IBS) with diarrhea
tinidazole (Tindamax®) ⁸	generic, Mission Pharm	Trichomoniasis Giardiasis (patients > 3 years old) Amebiasis (patients > 3 years old) Bacterial vaginosis in non-pregnant adult women
vancomycin (Vancocin®) ⁹	ViroPharma	Oral treatment of enterocolitis caused by <i>Staphylococcus aureus</i> [including methicillin-resistant <i>S. aureus</i> (MRSA)] and <i>C. difficile</i> associated diarrhea

*Suspension is not bioequivalent to the tablets

OVERVIEW

Organisms causing diarrhea and infections treated by the drugs included in this review are briefly described below. Other conditions treated by drugs in this class include hepatic encephalopathy (HE), bacterial vaginosis, and pre-operative bowel cleansing.

Amebiasis

Entamoeba histolytica is well recognized as a pathogenic ameba, associated with intestinal and extraintestinal infections.¹⁰ Patients can have an asymptomatic infection in mild cases. In severe cases, fulminant colitis and peritonitis or extraintestinal amebiasis can result. Amebia infections are acquired by the fecal-oral route either through person-to-person contact or indirectly through eating or drinking fecally-contaminated food or water. The parasite initially infects the colon and the incubation period is generally 2 to 4 weeks. Diarrhea is the most common symptom and can worsen to painful, bloody bowel movements, with or without fever (amebic dysentery). The majority of *E. histolytica* infections, morbidity, and mortality occur in Africa, Asia, and Central and South America.

Paromomycin or iodoquinol are the drugs of choice for treatment of asymptomatic infections proven to be caused by *E. histolytica*. For symptomatic intestinal infection, or extraintestinal infections (e.g., hepatic abscess), the drugs of choice are metronidazole (Flagyl) or tinidazole (Tindamax), immediately followed by treatment with iodoquinol or paromomycin.

Giardiasis

Giardiasis is the most frequently diagnosed intestinal parasitic disease in the United States and is caused by *G. lamblia*.¹¹ Diagnosis is done by the detection of cysts or trophozoites in the feces, trophozoites in the small intestine, or by the detection of *Giardia* antigens in the feces. Patients with Giardiasis may experience mild or severe diarrhea or, in some instances, no symptoms at all. Fever is rarely present. Onset of symptoms is generally 1 to 2 weeks after inoculation. Occasionally, some will have chronic diarrhea over several weeks or months, with significant weight loss. Giardiasis can cause failure to absorb fat, lactose, vitamin A, and vitamin B12. *Giardia* is passed from the feces of an infected person or animal and may contaminate water or food. Person-to-person transmission may also occur in daycare centers or other settings where hand washing practices are poor.

Effective treatments for *Giardia* infection include metronidazole, tinidazole, and nitazoxanide (Alinia). Paromomycin is an alternative agent.

Cryptosporidiosis

Cryptosporidiosis is caused by the protozoan, *Cryptosporidium parvum*.¹² Intestinal cryptosporidiosis is characterized by severe watery diarrhea but may also be asymptomatic. Intestinal cryptosporidiosis is self-limiting in most otherwise healthy people. Some infected people are asymptomatic; in others, symptoms may range from mild to profuse diarrhea, with passage of 3 to 6 liters of watery stool per day. In some outbreaks involving day-care centers, diarrhea has lasted from 1 to 4 weeks. Dehydration is a major concern, particularly for pregnant women and young children and immunocompromised people in whom the infection becomes chronic.

Immune status has a strong influence on the severity and duration of symptoms and illness. In people with HIV/AIDS or other immunocompromising conditions, *C. parvum* infections may be severe, lifelong, and may contribute to their death.

The FDA has approved nitazoxanide for the treatment of cryptosporidiosis in immunocompetent people. Nitazoxanide has not been shown to be superior to placebo for the treatment of diarrhea caused by *Cryptosporidium parvum* in HIV-infected or immunodeficient patients. A small number of studies reflect administration with azithromycin or paromomycin are also options in this demographic.

Traveler's Diarrhea

Traveler's diarrhea is characterized by more than three loose stools in a 24-hour period.¹³ Symptoms usually include fever, nausea, vomiting, and abdominal cramping. Most illness will resolve spontaneously over 3 to 5 days.

Traveler's diarrhea is caused by bacterial enteropathogens: enterotoxigenic *E. coli*, enteroaggregative *E. coli*, *Salmonella* species, *Campylobacter* species, and *Shigella* species. Enterotoxigenic *E. coli* is the most common pathogen, accounting for up to one-third of etiologies. Ingesting contaminated food or water is the most common mode of acquisition.

Antibiotic chemoprophylaxis for traveler's diarrhea is discouraged for most travelers due to mounting bacterial resistance. Symptomatic self-treatment of traveler's diarrhea includes replacement of fluid losses, although traveler's diarrhea in adults is not usually dehydrating. Symptomatic treatment with bismuth subsalicylate reduces the number of stools by approximately 50%. Other self-treatment options include loperamide, opiates, and diphenoxylate.

Antibiotic therapy includes fluoroquinolones, azithromycin, and rifaximin (Xifaxan). Agents no longer recommended due to drug resistance include neomycin, sulfonamides, ampicillin, doxycycline, tetracycline, and trimethoprim.

IDSA expects to publish updated guidelines for diarrhea in Fall 2016.

Clostridium difficile-associated Diarrhea

Clostridium difficile infection in adults is diagnosed by the presence of symptoms, usually diarrhea, and either a stool test positive for *C. difficile* toxins or toxigenic *C. difficile*, or colonoscopic or histopathologic findings of pseudomembranous colitis.¹⁴ *C. difficile*-associated diarrhea (CDAD) occurs in patients with an alteration in the microflora of the colon or after the exposure and ingestion of spores and vegetative cells.¹⁵ *C. difficile* multiplies in the colon and produces toxins that stimulate a response from the host to release tumor necrosis factor and interleukins, and to recruit neutrophils and monocytes. Colonic epithelial cell junctions widen, and cell death occurs. Additionally, production of hydrolytic enzymes leads to colitis and pseudomembrane formation in some patients. These changes in the colon cause watery and, occasionally, bloody diarrhea.

Risk factors for CDAD include prior antimicrobial use, even after the antimicrobial has been discontinued. Nearly all antibiotics have been associated with the development of CDAD. Other risk factors for CDAD include hospitalization, particularly in intensive care units, proton pump inhibitor use, advanced age (> 65 years old), in intensive care, immunosuppression, and gastrointestinal procedures.

A new hypervirulent North American Pulsed Field type 1 (NAP-1/B1/027) strain of *C. difficile* has emerged in North America and Europe.¹⁶ The rapidly increasing numbers of cases and deaths are partly related to the emergence of the NAP-1 strain of *C. difficile*.¹⁷ Unlike other strains, the NAP-1 strain is resistant to fluoroquinolones, so widespread fluoroquinolone use is likely a contributing factor.

Antibiotics should be discontinued as soon as possible, upon suspected *C. difficile* infection. If possible, avoid the use of antiperistaltic agents, as they may obscure symptoms and precipitate toxic megacolon. The 2010 Society for Healthcare Epidemiology of America (SHEA) and Infectious Diseases Society of America (IDSA) guidelines on *C. difficile* infection in adults recommend oral metronidazole as the drug of choice for the initial episode of mild-to-moderate *C. difficile* infection (Strength of recommendation: A; Level of Evidence: 1). Oral vancomycin is the drug of choice for an initial episode of severe *C. difficile* infection (Strength of recommendation: B; Level of Evidence: 1).¹⁸ Recurrent *C. difficile* infection is generally treated with the same regimen as for the initial episode (Strength of recommendation: A; Level of Evidence: 2), but severity of the recurrent episode should be considered in treatment decisions. Metronidazole should not be used beyond the first recurrence for *C. difficile* infection or for long-term chronic use due to the potential for cumulative neurotoxicity (Strength of recommendation: B; Level of Evidence: 2). Vancomycin is recommended for the first recurrence in patients with a white blood cell count $\geq 15,000$ cells/mL or a rising serum creatinine level, since they are at higher risk of developing complications. Treatment of second or later recurrence of *C. difficile* infection with vancomycin therapy is preferred. An update to these guidelines is projected to be available **Spring 2016**.

Bacterial Vaginosis

Bacterial vaginosis (BV) is a common vaginal infection in which the normal flora, *Lactobacillus* species, are replaced by overgrowth of several other microorganisms.¹⁹ Diagnosis is based on either gram staining of vaginal fluid or presence of at least three of the following criteria: vaginal discharge, vaginal pH > 4.5, positive whiff test, and the presence of clue cells. Risk factors for BV include having a new sexual partner or multiple sexual partners, douching, use of an intrauterine device, and lack of condom during sexual intercourse. Some patients do not experience symptoms; if symptoms are present, they can often be confused with those of a yeast infection. All women who have symptomatic disease require treatment. The **2015** Centers for Disease Control and Prevention (CDC) Sexually Transmitted Disease (STD) Treatment guidelines recommend the following treatment options: oral metronidazole, or intravaginal metronidazole gel or clindamycin cream or ovule.²⁰ Alternative treatment regimens include oral tinidazole or clindamycin. Clindamycin cream is oil-based and might weaken latex condoms and diaphragms for five days after use. Topical clindamycin preparations should not be used in the second half of pregnancy. Metronidazole ER is FDA approved for the treatment of BV; however, this formulation is not included in the CDC guidelines. **For this infection, the treatment recommendations have not changed from the previous iteration of the guidelines.**

Trichomoniasis

Trichomoniasis is caused by the protozoan *Trichomonas vaginalis*. Many infected women have symptoms characterized by a diffuse, malodorous, vaginal discharge with vulvar irritation. Diagnosis of vaginal trichomoniasis is usually performed by microscopy of vaginal secretions. The **2015** CDC STD treatment guidelines recommend a single oral dose of either metronidazole 2 g or tinidazole 2 g.²¹ An alternative regimen is metronidazole 500 mg orally twice daily for 7 days. The sexual partner should also be treated at the same time. **For this infection, the treatment recommendations have not changed from the previous iteration of the guidelines.**

Hepatic Encephalopathy/Coma

Hepatic encephalopathy occurs in patients with cirrhosis and is characterized by altered consciousness and behavior. Hepatic encephalopathy is caused by accumulation of nitrogenous substances, primarily ammonia, in the blood. In advanced stages, it is referred to as hepatic coma which may be preceded by seizures. The treatment goal is to reduce nitrogen load from the GI tract and to improve central nervous system (CNS) status. Treatment options include lactulose administered orally or by nasogastric tube or enema, non-absorbable antibiotics, and protein-restricted diets.^{22,23} Antibiotics are usually second-line therapy.²⁴ Neomycin or paromomycin can suppress the normal bacterial flora in the intestines that produce urease, an enzyme which breaks down urea to carbon dioxide and ammonia.²⁵ Rifaximin is minimally absorbed and affects the normal bacterial flora of the intestines.²⁶ In severe cases of hepatic encephalopathy, combination therapy can be considered. In clinical trials with rifaximin, 91% of patients also received concurrent lactulose therapy for the management of hepatic encephalopathy.

Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a functional bowel disorder which can be chronic, relapsing, and often life long.^{27,28} IBS occurs in up to 15% of the population and is up to 2.5 times more common in women than men. IBS is characterized by symptoms of abdominal pain or discomfort associated with abnormal stool frequency, abnormal stool form, abnormal stool passage, and/or bloating or abdominal distension, which may or may not be relieved by defecation at least 3 days per month in the past 3 months. Patients present with a combination of symptoms that are typically constipation predominant (IBS-C), diarrhea predominant (IBS-D), and/or alternating between both, or mixed (IBS-M). IBS is a chronic condition without a cure. Therefore, treatment of IBS is based on management of the patient's symptoms and may require a combination of modalities to achieve relief. The 2014 American Gastroenterological Association (AGA) guidelines on the treatment of IBS recommend rifaximin (Xifaxan) and loperamide over no drug treatment in patients with IBS-D.²⁹

PHARMACOLOGY^{30,31,32,33,34,35,36,37,38}

The antibiotics in this category treat a variety of different infections and conditions.

Nitazoxanide (Alinia) is a synthetic thiazolide antiprotozoal agent for the treatment of cryptosporidiosis or giardiasis. Nitazoxanide works by interfering with the pyruvate ferredoxin oxidoreductase (PFOR) enzyme-dependent electron transfer reaction which is essential for anaerobic energy metabolism. The PFOR enzyme from *G. lamblia* directly reduces nitazoxanide by transfer of electrons in the absence of ferredoxin. The PFOR enzyme is similar in *G. lamblia* and *C. parvum*. The PFOR enzyme interference may not be the only mechanism of action for nitazoxanide. Nitazoxanide and the active metabolite, tizoxanide, are active *in vitro* against the sporozoites and oocysts of *C. parvum* and the trophozoites of *G. lamblia*.

Neomycin and paromomycin are aminoglycoside antibiotics with bactericidal activity. Both agents are poorly absorbed from the GI tract. Neomycin is not used for systemic therapy, as it has been associated with irreversible ototoxicity. Aminoglycosides act by inhibiting bacterial protein synthesis through irreversible binding to the 30S ribosomal subunit of susceptible bacteria. Drug is actively transported into the bacterial cell where it binds to receptors present on the 30S ribosomal subunit. This binding interferes with the initiation complex between the messenger RNA and the subunit. As a result, due to

misreading of the bacterial DNA, abnormal nonfunctional proteins are formed, leading to bacterial cell death.

In the adjunctive treatment of hepatic encephalopathy or coma, neomycin and paromomycin are used to suppress growth of bacteria in the gut that produce urease, an enzyme that breaks down urea into carbon dioxide and ammonia. Decreasing the amount of ammonia available for absorption from the gut results in decreased serum and CNS levels and clinical improvement. Organisms susceptible to neomycin and paromomycin include *E. coli*, *Klebsiella*, and other *Enterobacteriaceae*. Like other aminoglycosides, neomycin and paromomycin are ineffective against anaerobic bowel flora.

Metronidazole (Flagyl, Flagyl ER) is a 5-nitroimidazole agent with excellent anaerobic bacterial activity. It is effective against protozoa such as *T. vaginalis*, *E. histolytica*, and *G. lamblia*. Metronidazole can also be used as a component of multiple regimens to treat *Helicobacter pylori*. Both the parent compound and the metabolite have *in vitro* bactericidal activity against most anaerobic bacteria, including *Bacteroides* species and *Fusobacterium* species; anaerobic Gram-positive bacilli including *Clostridium* species; and anaerobic Gram-positive cocci, including *Peptococcus niger* and *Peptostreptococcus* species.

Tinidazole (Tindamax) is a 5-nitroimidazole anti-protozoal agent similar to metronidazole with similar efficacy to metronidazole against protozoa such as *T. vaginalis*, *E. histolytica*, and *G. lamblia*. Tinidazole has a shorter duration of therapy for some indications. Tinidazole is also effective against anaerobic bacteria and has been used clinically for prophylaxis and treatment of infections due to anaerobic bacteria. The nitro-group of tinidazole is reduced by cell extracts of *Trichomonas*. Free nitro-radicals generated as a result of the reduction may be responsible for the antiprotozoal activity. In addition, chemically reduced tinidazole releases nitrites that cause damage to bacterial DNA. The mechanism of action against *Giardia* sp. and *Entamoeba* sp. is unknown.

Rifaximin (Xifaxan) is a non-aminoglycoside semi-synthetic antibacterial derived from rifamycin SV.³⁹ It acts by binding to the beta-subunit of bacterial DNA-dependent RNA polymerase, resulting in inhibition of bacterial RNA synthesis. Rifaximin is minimally absorbed and concentrated in the gastrointestinal tract. Rifaximin has a low risk of inducing bacterial resistance with a low incidence of serious adverse effects which makes rifaximin useful in the long-term management of hepatic encephalopathy.

Vancomycin is a glycopeptide antibiotic obtained from *Nocardia orientalis* and is effective only for Gram-positive bacteria. Its bactericidal action against *Staphylococcus aureus* and *Clostridium difficile* is primarily due to inhibition of cell-wall biosynthesis; it also alters bacterial-cell-membrane permeability and RNA synthesis. Vancomycin is poorly absorbed in the GI tract and is administered orally to treat GI infections, such as pseudomembranous colitis, due to overgrowth of *Clostridium difficile*. Resistance to vancomycin can occur. The exact mechanism of *S. aureus* resistance may be due to cell wall thickening and transfer of genetic material. The mechanism that causes *C. difficile* resistance is not fully understood.

Fidaxomicin (Dificid) is a macrolide antibacterial agent that exerts its effects via inhibiting RNA synthesis. This agent is a fermentation product obtained from the actinomycete *Dactylosporangium aurantiacum*. It acts locally in the gastrointestinal tract on *C. difficile*; it should not be used for systemic infections, nor for infections caused by any organism other than *C. difficile*. Fidaxomicin has little or no activity against organisms other than clostridia, allowing for preservation of normal gastrointestinal flora. Fidaxomicin is bactericidal against *C. difficile*; vancomycin and metronidazole are bacteriostatic.

In vitro studies indicate a low frequency of spontaneous resistance of *C. difficile* to fidaxomicin and no *in vitro* cross-resistance with other classes of antibacterial drugs.

An *in vitro* study found that fidaxomicin inhibited *C. difficile* spore formation, while vancomycin, metronidazole, and rifaximin did not.⁴⁰ This inhibitory effect on *C. difficile* sporulation is thought to lend fidaxomicin its performance in both sustained clinical response and reduced recurrence of infection. In whole genome sequencing of *C. difficile* strains, in recurrence of infection in those patients previously treated with fidaxomicin, both relapse and reinfection with *C. difficile* were reduced with fidaxomicin.⁴¹

Reports of *in vitro* susceptibility profile of nosocomial and community acquired pathogens should aid prescribers in selecting appropriate antimicrobial drug therapy.

PHARMACOKINETICS^{42,43,44,45,46,47,48,49}

Drug	Bioavailability (%)	Half-life (hours)	Metabolites	Elimination (%)
fidaxomicin (Dificid)	minimal systemic absorption	11.7	1 active metabolite	Feces: 92
metronidazole (Flagyl)	nr	8	3 metabolites	Urine: 60-80 Feces: 6-15
metronidazole ER (Flagyl ER)	nr	8	3 metabolites	Urine: 60-80 Feces: 6-15
neomycin	3	nr	nr	Feces: 97
nitazoxanide (Alinia)	nr	nr	tizoxanide (active); tizoxanide glucuronide	Urine: 33.3 Feces: 66.7
paromomycin	poor oral absorption	nr	nr	Feces: 100
rifaximin (Xifaxan)	low absorption	0.8-4.8	nr	Urine: 0.32 Feces: 96.62
tinidazole (Tindamax)	completely absorbed	12-14	significant metabolism; 2-hydroxymethyl metabolite appears in plasma	Urine: 20-25 Feces: 12
vancomycin (Vancocin)	poor systemic absorption	nr	nr	Feces

nr = not reported

Nitazoxanide (Alinia) tablets and suspension are not bioequivalent. The relative bioavailability of the suspension compared to the tablet is 70%. Absorption of nitazoxanide is nearly doubled in the presence of food. Nitazoxanide dosage forms should be administered with food. Nitazoxanide's active metabolite tizoxanide is highly protein bound (> 99.9%).

Patients with colitis may develop detectable serum vancomycin (Vancocin) levels following oral administration, especially if they have renal impairment.

CONTRAINDICATIONS/WARNINGS^{50,51,52,53,54,55,56,57,58}

Almost all antibacterial agents have been associated with pseudomembranous colitis (antibiotic-associated colitis), which may range in severity from mild to life-threatening. Systemic use of

antibiotics predisposes patients to development of pseudomembranous colitis. Consideration should be given to the diagnosis of pseudomembranous colitis in patients presenting with diarrhea during or following antibacterial therapy. If diarrhea develops during therapy, the drug should be discontinued, and, if diagnosis of pseudomembranous colitis is confirmed, therapeutic measures should be instituted. Drugs inhibiting peristalsis are contraindicated if pseudomembranous colitis exists.

Neomycin and paromomycin are contraindicated for use in patients with GI obstruction, ileus, or ulcerative bowel lesions, including ulcerative colitis. Absorption may be increased in the presence of lesions and potentially result in increased adverse effects, such as ototoxicity (sometimes irreversible) and nephrotoxicity, which are more likely to occur with systemic aminoglycoside therapy. Patients receiving oral neomycin and paromomycin should be monitored closely for ototoxicity and nephrotoxicity, as systemic absorption can occur. Nephrotoxicity is evident by decreased creatinine clearance, the presence of cells or casts, oliguria, proteinuria, decreased urine specific gravity, or evidence of increasing nitrogen retention (increasing blood urea nitrogen [BUN] or serum creatinine). Nephrotoxicity is generally reversible. Aminoglycosides are also associated with neuromuscular blockade and respiratory paralysis; neuromuscular weakness can last hours to days. Use with caution in patients with muscular disorders, such as myasthenia gravis or Parkinson's Disease. Patients with hypersensitivities to any of the aminoglycosides should not receive neomycin or paromomycin.

Vancomycin (Vancocin) oral capsules are not for the treatment of systemic infections as oral vancomycin is not significantly systemically absorbed. However, patients with inflammation of the intestinal mucosa may have significant systemic absorption; monitoring of serum levels and adverse effects may be appropriate in some, particularly those with renal impairment. Parenteral administration of vancomycin for the treatment of colitis is not effective. Oral vancomycin is contraindicated in patients with a known hypersensitivity to vancomycin.

Nephrotoxicity and ototoxicity have also been reported during and/or following oral vancomycin therapy. Assessment of renal and auditory function may be appropriate in some instances.

Rifaximin (Xifaxan) is contraindicated in patients with a hypersensitivity to rifaximin, or any of the rifamycin antimicrobial agents. Hypersensitivity reactions have included exfoliative dermatitis, angioneurotic edema, and anaphylaxis. Rifaximin should not be used to treat patients with diarrhea complicated by fever or blood in the stool or diarrhea secondary to pathogens other than *E. coli* due to a lack of proven effectiveness. Rifaximin has not been shown to be effective in cases of traveler's diarrhea due to *Campylobacter jejuni*, *Shigella* species, or *Salmonella* species and should not be used if one of these organisms may be suspected as the causative pathogen. Rifaximin should be discontinued if diarrhea symptoms worsen or persist more than 24 to 48 hours. Rifaximin is poorly absorbed into the systemic circulation and should not be used to treat systemic infections. In patients with severe hepatic impairment, an increased systemic exposure of rifaximin can occur. Caution should be used for administering rifaximin to patients with severe hepatic impairment (Child-Pugh C). Caution should be used when administering rifaximin along with a P-glycoprotein (P-gp) inhibitor due to the possibility of a substantial increase in exposure to rifaximin.

Nitazoxanide (Alinia) is contraindicated in patients with prior hypersensitivity to nitazoxanide or any of the product components. Nitazoxanide oral suspension contains 1.48 grams of sucrose per 5 mL; diabetic patients and their caregivers should be aware of the sucrose content.

Metronidazole (Flagyl, Flagyl ER) and tinidazole (Tindamax) are contraindicated in patients with a prior history of hypersensitivity to nitroimidazole derivatives. A black box warning appears in the labeling for metronidazole that its use has been shown to be carcinogenic in mice and rats. A similar warning appears in the labeling for tinidazole (Tindamax) as these agents are structurally related and have similar biological effects. Use of each agent should be limited to approved indications.

Tinidazole and metronidazole are contraindicated during the first trimester of pregnancy. Convulsive seizures, encephalopathy, aseptic meningitis, and optic and peripheral neuropathy have been reported in patients receiving metronidazole and/or tinidazole. Therapy should be withdrawn if abnormal neurological signs develop. The manufacturer's of metronidazole (Flagyl, Flagyl ER) recommend caution in patients with existing CNS disorders.

Use metronidazole and tinidazole with caution in patients with blood dyscrasias. Tinidazole may produce transient leukopenia and neutropenia.

Metronidazole and tinidazole may alter reported values of laboratory tests, such as aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), lactate dehydrogenase (LDH), triglycerides, and hexokinase glucose.

Metronidazole is also contraindicated in the presence of alcohol; do not consume alcohol or products containing propylene glycol during and for at least 3 days after completing metronidazole use. Do not use metronidazole in patients who have taken disulfiram within 2 weeks.

There have been reports of acute hypersensitivity reactions (angioedema, dyspnea, pruritus, and rash). In the event of a severe reaction, discontinue use. Do not use for systemic infections. Fidaxomicin (Dificid) should not be used in patients who have had prior hypersensitivity reaction to the drug.

Prescribing vancomycin, fidaxomicin, rifaximin, metronidazole, or tinidazole in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug resistant bacteria.

DRUG INTERACTIONS^{59,60,61,62,63,64,65}

Tizoxanide, the active metabolite of nitazoxanide (Alinia), is highly bound to plasma protein (>99.9%). Therefore, caution should be used when administering nitazoxanide concurrently with other highly plasma protein-bound drugs with narrow therapeutic indices, such as warfarin. Nitazoxanide and tizoxanide do not have any significant inhibitory effects on the CYP 450 system.

Due to the low systemic absorption of rifaximin (Xifaxan), drug interactions with the CYP450 enzymes are not expected. Limited studies with midazolam and oral contraceptives have not shown any drug interactions with rifaximin.⁶⁶

Metronidazole (Flagyl, Flagyl ER) and tinidazole (Tindamax) can potentiate the anticoagulant effect of warfarin and other oral coumarin anticoagulants, resulting in a prolonged prothrombin time and altered international normalized ratio (INR). Anticoagulant therapy may require close monitoring and dosage adjustment for up to 8 days after discontinuation of tinidazole.

Co-administration of drugs that induce CYP450 enzymes, such as phenobarbital and phenytoin, may accelerate the elimination of metronidazole or tinidazole resulting in reduced plasma levels of the antibiotic.

Metronidazole has been shown to decrease the clearance of 5-fluorouracil, cyclosporine, and tacrolimus which can lead to toxicity, and tinidazole is expected to show similar effects. Monitor the toxicities of cyclosporine, tacrolimus, and fluorouracil with concurrent use of metronidazole or tinidazole. Impaired clearance of phenytoin by metronidazole has also been reported.

Inhibitors of the CYP450 system, such as cimetidine, may prolong the half-life of metronidazole and tinidazole.

In patients on relatively high doses of lithium, short-term metronidazole therapy has been associated with elevation of serum lithium. Since tinidazole is structurally related to metronidazole, it may have a similar effect. Serum lithium and serum creatinine levels should be obtained several days after beginning metronidazole or tinidazole to detect any increase that may precede clinical symptoms of lithium toxicity.

Cholestyramine has the potential to decrease the oral absorption of metronidazole and tinidazole. Oral doses should be separated with concurrent use.

Alcoholic beverages should not be consumed during metronidazole or tinidazole therapy and for at least 3 days afterward because abdominal cramps, nausea, vomiting, headaches, and flushing may occur. Metronidazole and tinidazole should not be given to patients who have taken disulfiram within the last 2 weeks as psychotic reactions have been reported with concurrent use.

Paromomycin and neomycin can reduce digoxin absorption by up to 28%. Monitor the clinical response of the patient and consider monitoring serum digoxin concentration with prolonged antibiotic therapy. Oral administration of these agents inhibit vitamin K-synthesizing intestinal bacteria and can potentiate the effects of warfarin. Either agent given orally can reduce the bioavailability of methotrexate; oral neomycin has been shown to reduce the bioavailability of oral penicillin V, oral vitamin B-12, methotrexate, and 5-fluorouracil.

Antibiotics that reduce colonic flora may theoretically interfere with the biological conversion of lactulose to its active, acidic products. Since neomycin is also used in the treatment of hepatic encephalopathy, concurrent use may interfere with the effectiveness of lactulose. Neomycin and lactulose have been used together successfully, as long as the fecal pH remains < 6, and the combination is recommended in patients who respond poorly to therapy with lactulose alone. Patients taking both drugs concurrently should be monitored for the possibility of a decreased response to lactulose.

Fidaxomicin (Dificid) and its active metabolite are substrates of P-gp, and can have slightly higher plasma concentrations in the presence of cyclosporine, as cyclosporine has an inhibitive effect on P-gp transporters. The increased concentration is not significant and no dosage adjustment is necessary.

Drug interaction studies have not been performed for orally administered vancomycin (Vancocin).

ADVERSE EFFECTS^{67,68,69,70,71,72,73,74}

Drug	Abdominal Pain	Headache	Diarrhea	Nausea	Metallic Taste
fidaxomicin (Difacid)	6	nr	nr	11	nr
metronidazole (Flagyl)	reported	reported	reported	12	reported
metronidazole ER (Flagyl ER)	4	18	4	10	9
neomycin	nr	nr	reported	reported	nr
nitazoxanide (Alinia) oral suspension n=613	7.8	1.1	2.1	< 1	nr
nitazoxanide (Alinia) tablets n=1,628	6.7	3.1	4.3	3.1	nr
paromomycin	reported	reported	reported	reported	nr
rifaximin (Xifaxan) n=320 with traveler's diarrhea	7 (10)	10 (9)	< 2	5 (8)	Loss of taste < 2
rifaximin (Xifaxan) n=140 with hepatic encephalopathy	9 (8)	reported	nr	14 (13)	nr
tinidazole (Tindamax) 2 gm single dose – multi-day dose	> 1	0.7-1.3	reported	3.2-4.5	3.7-6.3
vancomycin (Vancocin)	15	7	nr	17	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

Common adverse effects for vancomycin (Vancocin) also include hypokalemia (13%), vomiting and pyrexia (9%). Adverse effects such as nephrotoxicity, ototoxicity, neutropenia, and thrombocytopenia are more commonly associated with intravenous (IV) administration of vancomycin.

Prolonged oral neomycin therapy has been associated with a malabsorption syndrome, characterized by steatorrhea, decreased serum carotene, and decreased xylose absorption.

Other common adverse effects experienced with fidaxomicin therapy are vomiting (7%), GI hemorrhage (4%), anemia, and neutropenia (each 2%).

Other common adverse reactions reported with rifaximin include; flatulence, rectal tenesmus, and defecation urgency when used for travelers diarrhea. When used for HE, peripheral edema, fatigue, ascites, and flatulence have been reported as the most common adverse reactions. **When used for IBS with diarrhea, increase in ALT.**

SPECIAL POPULATIONS^{75,76,77,78,79,80,81,82}

Pediatrics

Safety and effectiveness of metronidazole ER (Flagyl ER), fidaxomicin (Dificid), and oral vancomycin (Vancocin) in pediatric patients have not been established. The safety and effectiveness of metronidazole (Flagyl) have not been established in pediatric patients, except for the treatment of amebiasis.

Nitazoxanide (Alinia) tablets have not been studied in children less than 12 years of age. A single nitazoxanide tablet contains a greater amount of nitazoxanide than is recommended for pediatric patients 11 years and younger and should not be used in this age group. Nitazoxanide oral suspension has not been studied in children less than 1 year of age.

Safety and effectiveness of rifaximin (Xifaxan) for treatment of traveler's diarrhea have not been established in children less than 12 years of age. For hepatic encephalopathy, safety and effectiveness of rifaximin have not been established in patients less than 18 years of age. For IBS with diarrhea, safety and effectiveness has not been established in patients under age 18.

Safety and effectiveness of neomycin have not been established in pediatric patients. Various drug information sources can provide dosing information for pediatric patients; however, large, well-designed, formal clinical trials have not been performed. Paromomycin is indicated in the pediatric population for treatment of intestinal amebiasis.

Tinidazole (Tindamax) has only been studied in children age 3 years and older for the treatment of giardiasis and amebiasis.

Pregnancy

Metronidazole and tinidazole are contraindicated during the first trimester of pregnancy. Both agents readily cross the placental barrier and enter the fetal circulation rapidly.

Metronidazole, oral vancomycin, fidaxomicin, and nitazoxanide are classified as Pregnancy Category B. Rifaximin, paromomycin, and tinidazole are Pregnancy Category C. Neomycin is Pregnancy Category D.

Renal Impairment

Pharmacokinetic studies of nitazoxanide and rifaximin have not been performed in patients with renal insufficiency.

If tinidazole is administered the same day and prior to hemodialysis, administer an additional half dose after hemodialysis.

No dose adjustment for metronidazole or fidaxomicin is warranted for patients with impaired renal function.

Since neomycin and paromomycin are excreted renally and are nephrotoxic, caution should be used when administering these agents to patients with renal impairment.

Hepatic Impairment

Since rifaximin acts locally in the GI tract, no dosage adjustment is necessary in patients with hepatic impairment. However, there is potential for increased systemic exposure of rifaximin with severe hepatic impairment; therefore, caution should be used when prescribing rifaximin to patients with severe hepatic impairment (Child-Pugh C).

Elimination of fidaxomicin and its metabolite is not expected to be affected by hepatic impairment. No dosage adjustment is necessary with hepatic impairment.

Pharmacokinetic studies of nitazoxanide and tinidazole have not been performed in patients with hepatic insufficiency. Use caution when administering nitazoxanide and tinidazole to patients with hepatic impairment.

Patients with severe hepatic disease metabolize metronidazole slowly, with resultant accumulation of metronidazole and its metabolites in the plasma. A lower dose than usually recommended should be considered for patients with severe hepatic disease.

Geriatric Patients

Studies with nitazoxanide, rifaximin for traveler's diarrhea, and tinidazole did not include a sufficient number of patients aged 65 years and older. For rifaximin for hepatic encephalopathy, no overall differences in safety or effectiveness were observed between older and younger patients.

The elderly (> 65 years) and patients with dehydration are at an increased risk of toxicity associated with neomycin.

For geriatric patients (> 65 years) on oral vancomycin, regardless of renal status, it is recommended that renal function be monitored during and following treatment in this population to detect possible nephrotoxicity.

There were no differences in safety or efficacy of fidaxomicin between older (≥ 65 years) and younger patients. No dose adjustment is necessary with fidaxomicin in elderly patients.

HIV-infected Patients

According to the prescribing label, nitazoxanide (Alinia) tablets and suspension have not been studied in the treatment of diarrhea caused by *G. lamblia* in immunodeficient patients, including HIV-infected patients. Nitazoxanide has not been shown to be superior to placebo for the treatment of diarrhea caused by *C. parvum* in HIV-infected or immunodeficient patients.

In a manufacturer-sponsored, compassionate-use study based in the United States, nitazoxanide has been shown to be useful in the management of cryptosporidiosis in patients with acquired immune deficiency syndrome (AIDS).⁸³ A total of 365 patients (at least 3 years of age) with documented cryptosporidiosis-positive stools and diarrhea were given nitazoxanide 500 to 1,500 mg twice daily. Therapy duration was a median of 62 days. For the patients (n=357) included in the intent-to-treat analysis, 59% achieved a sustained clinical response while on treatment. Clinical responses correlated with *C. parvum* negative stools ($p<0.0001$). No safety issues were noted.

In a study performed in Mexico, patients with HIV with diarrhea due to *C. parvum* were enrolled in a double-blind trial to investigate the safety and efficacy of nitazoxanide in cryptosporidiosis.⁸⁴ Patients were randomized to placebo or nitazoxanide 500 mg or 1,000 mg twice daily for 14 days. Patients then crossed over to the alternative (active drug or placebo) treatment. Both nitazoxanide groups produced cure rates (defined as no identified *C. parvum* oocysts post-treatment stool examinations) superior to placebo of 63% (p=0.016) for the low-dose nitazoxanide group and 67% (p=0.013) for the high-dose nitazoxanide group. Complete diarrhea resolution occurred in 86% of patients considered to have no *C. parvum* oocysts on stool examination. Both doses of nitazoxanide were well tolerated.

Paromomycin is not FDA-approved but is used for the treatment of cryptosporidiosis in HIV-infected patients.⁸⁵

DOSAGES^{86,87,88,89,90,91,92,93}

Drug	Adult Dosing	Pediatric Dosing	Availability
fidaxomicin (Dificid)	Diarrhea caused by <i>C. difficile</i> (> 18 years): One 200 mg tablet orally twice daily for 10 days with or without food	--	200 mg tablet
metronidazole (Flagyl)	Trichomoniasis: 375 mg twice daily for 7 days or 250 mg 3 times daily for 7 days Alternative; 2 g either as a single dose or in 2 divided doses of 1 g each given in the same day Amebiasis – intestinal infection: 750 mg 3 times daily for 5 to 10 days Amebiasis – liver abscess: 500 mg or 750 mg 3 times daily for 5 to 10 days Anaerobic infections: 7.5 mg/kg every 6 hours (~ 500 mg for a 70-kg adult); do not exceed 4 g in 24-hour period Duration of therapy is 7 to 10 days, depending on severity of infection	Amebiasis: 35 to 50 mg/kg/day divided into 3 doses for 10 days	375 mg capsule 250, 500mg tablet
metronidazole ER (Flagyl ER)	Bacterial Vaginosis: 750 mg once daily for 7 days under fasting conditions; take at least 1 hour before or 2 hours after meals	--	750 mg tablet
neomycin	Pre-operative bowel preparation: 1 g by mouth every hour for 4 doses, then 1 g every 4 hours for the remainder of 24 hours If given with erythromycin, give pre-operative doses for 3 doses in the 24 hours immediately prior to surgery Adjunctive treatment of hepatic encephalopathy: 1 to 3 g orally every 6 hours for 5 to 6 days	--	500 mg tablet
nitazoxanide (Alinia)	Diarrhea caused by <i>G. lamblia</i> or <i>C. parvum</i> (> 12 years): 500 mg tablet every 12 hours with food for 3 days OR 500 mg (25 mL) of oral suspension every 12 hours with food for 3 days	Diarrhea caused by <i>G. lamblia</i> or <i>C. parvum</i> – oral suspension: 1-3 years: 100 mg (5 mL) of oral suspension every 12 hours with food for 3 days 4-11 years: 200 mg (10 mL) of oral suspension every 12 hours with food for 3 days ≥ 12 years: 500 mg (1 tablet) every 12 hours for 3 days OR 500 mg (25 mL) of oral suspension every 12 hours with food for 3 days	500 mg tablet 100 mg/5 mL oral suspension

Dosages (continued)

Drug	Adult Dosing	Pediatric Dosing	Availability
paromomycin	Amebiasis, Intestinal: 25 to 35 mg/kg/day, administered in 3 divided doses with meals, for 5 to 10 days Hepatic coma: 4 g daily in divided doses, given at regular intervals for 5 to 6 days	Amebiasis, Intestinal: 25 to 35 mg/kg/day, administered in 3 divided doses with meals, for 5 to 10 days	250 mg capsules
rifaximin (Xifaxan)	Traveler's diarrhea: 200 mg 3 times daily for 3 days taken with or without food Reduction in risk of overt hepatic encephalopathy: 550 mg twice daily taken with or without food Irritable Bowel Syndrome with Diarrhea: 550 mg 3 times daily for up to 14 days May repeat course twice more for a maximum of 3 treatment cycles	--	200, 550 mg tablets
tinidazole (Tindamax)	Trichomoniasis: 2 g as a single dose taken with food; treat sexual partners with the same dose and at the same time Giardiasis: 2 g as a single dose taken with food Amebiasis, Intestinal: 2 g daily for 3 days with food Amebic liver abscess: 2 g daily for 3 to 5 days with food Bacterial vaginosis (non-pregnant females): 2 g once daily for 2 days taken with food or 1 g once daily for 5 days taken with food	Giardiasis (> 3 years old): 50 mg/kg (up to 2 gm) as a single dose given with food Amebiasis (> 3 years old): 50 mg/kg/day (up to 2 g per day) for 3 days with food Amebic liver abscess (> 3 years old): 50 mg/kg/day (up to 2 g per day) for 3 to 5 days with food	250, 500 mg tablets
vancomycin (Vancocin)	C. difficile associated diarrhea: 125 mg orally 4 times daily for 10 days Staphylococcal enterocolitis: 500 mg to 2 g orally daily in 3 or 4 divided doses for 7 to 10 days	C. difficile associated diarrhea: 40 mg/kg/day given in 3 to 4 divided doses for 7 to 10 days (not to exceed 2 g per day) Staphylococcal enterocolitis: 40 mg/kg/day divided into 3 to 4 doses per day for 7 to 10 days (not to exceed 2 g per day)	125, 250 mg capsules

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials published in the last 10 years are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship funding must be considered, the studies in this review have also been evaluated for validity and importance.

Recent clinical studies regarding use of paromomycin for the treatment of intestinal amebiasis or hepatic coma are lacking.

fidaxomicin (Difcid) and vancomycin

Safety and efficacy comparisons were done between fidaxomicin and vancomycin when used to treat patients with *C. difficile* infection in Europe, Canada, and the United States. A randomized, double-blind, multicenter, non-inferiority trial was conducted by enrolling patients between April 2007 and December 2009. Patients enrolled were > 16 years of age and diagnosed with acute, toxin positive *C. difficile* infection. These patients were randomly assigned to receive 200 mg of fidaxomicin orally every 12 hours, or 125 mg vancomycin orally every 6 hours for 10 days. The primary endpoint was clinical cure, defined as resolution of diarrhea and no further need for treatment.

Of the 535 patients enrolled, 270 were assigned to the fidaxomicin group and 265 to vancomycin therapy. Twenty-six patients were excluded, leaving 509 in the modified intention-to-treat population. A total of 198 (91.7%) of 216 patients receiving fidaxomicin achieved clinical cure compared to 213 (90.6%) of 235 patients who were given vancomycin. This met the criteria for non-inferiority (one-sided 97.5 % confidence interval [CI], -4.3%). Subgroup analysis also showed outcomes in the 2 treatment groups did not differ significantly. Occurrences of treatment-emergent adverse events were also found to be similar.⁹⁴

Another study also compared fidaxomicin to vancomycin with the primary endpoint being the rate of clinical outcomes of *C. difficile* infection (CDI) treatment when advancing age is considered.⁹⁵ Regression modeling of results from 2 double-blind randomized multicenter studies on treatment outcomes of both primary and first recurrent cases for the effects of age was done. Cure was considered resolution of diarrhea, and recurrence was defined as diarrhea within 4 weeks of successful therapy. Participants were randomized into studies in the United States, Canada, and Europe, totalling 999 subjects. Those patients with toxin-positive CDI were randomized to receive fidaxomicin (200 mg twice daily x 10 days) or vancomycin (125 mg 4 times daily x 10 days). The participants were divided into groups of 18 to 40 years and in 10-year increments thereafter. Regression demonstrated a 17%

lower cure rate, 17% greater recurrence rate, and a 13% lower sustained clinical response rate would appear by advancing decade in those ≥ 40 ($p < 0.01$ each).

The results associated fidaxomicin treated patients with a more than 50% lower relative risk for recurrence than in those treated with vancomycin ($p < 0.001$). Fidaxomicin treatment was associated with a 60% lower risk of recurrence than vancomycin after adjusting for age, concomitant antibiotics, and *C. difficile* strain.⁹⁶

metronidazole (Flagyl) and vancomycin (Vancocin)

In a randomized, double-blind, placebo-controlled trial, 172 patients with *C. difficile*-associated diarrhea were stratified according to disease severity from mild to severe disease.⁹⁷ Patients were randomized to metronidazole 250 mg orally 4 times daily or oral vancomycin 125 mg 4 times daily for 10 days; a placebo was given to all patients in addition to the assigned drug. One-hundred fifty patients completed the trial. For patients with mild disease, treatment with metronidazole (90%) or vancomycin (98%) resulted in clinical cure ($p = 0.36$). For patients with severe disease, metronidazole treatment resulted in clinical cure in 76% of patients compared to 97% of patients receiving vancomycin ($p = 0.02$). Patients were followed up for 21 days to assess cure, treatment failure, relapse, or intolerance. Recurrence of clinical symptoms occurred in 15% and 14% of patients receiving metronidazole and vancomycin, respectively.

In a review of 39 articles (7,005 patients) by 2 independent reviewers, it was found that, in *C. difficile* infection (CDI) treated with oral metronidazole or vancomycin, there was a 22.4% failure rate with metronidazole compared to a failure rate of 14.2% with vancomycin oral treatment. The recurrence rate of CDI in patients treated with metronidazole was 27.1% compared to 24% for those patients treated with vancomycin.⁹⁸

neomycin – Pre-operative Administration

A study compared the use of prophylactic antibiotics, given orally or intravenously (IV), in addition to mechanical bowel cleansing in 300 patients undergoing elective colorectal resection surgery.⁹⁹ All patients underwent mechanical colon cleansing with oral sodium phosphate and IV antibiotic prophylaxis with cefoxitin given 1 hour pre-operatively and 2 post-operative doses. Patients were randomly assigned to 1 of 3 groups – A) 3 doses of oral neomycin and metronidazole at the time of mechanical bowel cleansing, B) 1 dose of oral neomycin and metronidazole, or C) no oral antibiotics. Follow-up occurred during the hospital stay, days 7, 14, and 30 post-surgery. Vomiting occurred in 31%, 11%, and 9% of groups A, B, and C, respectively ($p < 0.001$). Nausea was reported in 44%, 18%, and 13% of patients, respectively ($p < 0.001$). The incidence of wound infection, suture dehiscence, urinary infections, pneumonia, postoperative ileus, or intra-abdominal abscess did not differ among the groups.

nitazoxanide (Alinia) versus vancomycin

In a randomized, double-blind study, a total of 50 patients with CDI were randomized to receive either nitazoxanide ($n = 23$) or vancomycin ($n = 27$) for 10 days.¹⁰⁰ Initial response was the absence of all CDI symptoms between days 11 and 13, final response was the absence of all CDI symptoms by day 31. Time to resolution was similar in both groups who completed therapy, while both initial and final response was greater in the nitazoxanide treated group (77% initial response versus 74% with vancomycin; 95% CI, -24 to 28). Final response was 94% of those treated with nitazoxanide versus 87%

in the vancomycin group (95% CI, -18 to 30). It was concluded that nitazoxanide is as effective as vancomycin in treating CDI; due to the small study sample, conclusions as to noninferiority of nitazoxanide to vancomycin cannot be deduced.

nitazoxanide (Alinia) versus metronidazole (Flagyl)

A total of 110 children from Northern Peru were enrolled in a trial comparing nitazoxanide and metronidazole for the treatment of *Giardia intestinalis*.¹⁰¹ Patients were randomized to nitazoxanide 100 mg twice daily for 3 days for ages 2 to 3 years, nitazoxanide 200 mg twice daily for ages 4 to 11 years for a total of 3 days, metronidazole 125 mg twice daily for 5 days for ages 2 to 5 years, or metronidazole 250 mg twice daily for 5 days for ages 6 to 11 years. Diarrhea resolved in 85% and 80% of the nitazoxanide and metronidazole groups, respectively, at the day 7 follow-up visit. Most cases of diarrhea resolved within 4 days. Only minor adverse effects were reported.

rifaximin (Xifaxan) versus ciprofloxacin (Cipro)

A double-blinded trial evaluated rifaximin 400 mg twice daily and ciprofloxacin 500 mg twice daily for 3 days in 187 adult travelers to Mexico or Jamaica with diarrhea.¹⁰² The time from initiation of therapy to passage of last unformed stool was similar – median 25.7 hours versus 25 hours for rifaximin and ciprofloxacin, respectively. Clinical improvement in the first 24 hours of treatment was similar ($p=0.199$) as was failure to respond to treatment ($p=0.411$). Microbiological cure rate was similar between the groups ($p=0.222$). Incidence of adverse effects was similar in both groups. FDA-approved dosage of rifaximin is 200 mg 3 times a day for 3 days.

A randomized, double-blind trial compared rifaximin with placebo and ciprofloxacin for treatment of traveler's diarrhea.¹⁰³ Adult travelers ($n=399$) consulting travel clinics in Mexico, Guatemala, and India were randomized to receive rifaximin 200 mg 3 times a day, ciprofloxacin (500 mg 2 times a day and placebo once a day), or placebo 3 times a day for 3 days. Patients recorded daily diaries with the time and consistency of each stool and documented symptoms for 5 days after treatment. The median time to last unformed stool was 32 hours with rifaximin, 28.8 hours with ciprofloxacin ($p=0.0003$ versus placebo; $p=0.35$ versus rifaximin), and 65.5 hours with placebo ($p<0.0001$ versus rifaximin; risk ratio 1.6; 95% CI, 1.2 to 2.2).

rifaximin (Xifaxan) versus lactulose

A prospective, double-blind, randomized controlled trial consisting of 120 persons with overt hepatic encephalopathy (HE) were randomized into either Group A; lactulose plus rifaximin (1,200 mg/day; $n=63$) and Group B; (lactulose plus placebo; $n=57$).¹⁰⁴ The primary endpoint was complete reversal of HE; secondary endpoints were hospital stay and mortality. A total of 120 patients (mean age 39.4 ± 9.6 years; male/female ratio 89:31) were included in the study. A total of 37 (30.8%) patients were in Child-Turcotte-Pugh (CTP) class B and 83 (69.2%) were in CTP class C. Mean CTP score was 9.7 ± 2.8 and the MELD (model for end-stage liver disease) score was 24.6 ± 4.2 . At the time of admission, 22 patients (18.3%) had grade 2, 40 (33.3%) had grade 3, and 58 (48.3%) had grade 4 HE. Of the patients, 48 (76%) in group A compared with 29 (50.8%) in group B had complete reversal of HE ($p<0.004$). Group B (lactulose) had more deaths than did Group A (23.8% versus 49.1%; $p<0.05$), deaths due to sepsis were significantly higher in Group B (7/17; $p=0.01$), with no differences in death due to gastrointestinal bleed or hepatorenal syndrome. Patients in Group A (lactulose and rifaximin) had

shorter hospital stays, as well (5.8 ± 3.4 versus 8.2 ± 4.6 days, $p=0.001$). Therefore, it was concluded that, in cases of HE, the combination of lactulose and rifaximin is more effective than lactulose alone.

rifaximin (Xifaxan) versus neomycin

In a double-blind, randomized, controlled trial, the efficacy and tolerability of rifaximin and neomycin were compared in 49 patients with hepatic encephalopathy due to cirrhosis.¹⁰⁵ Patients were randomized to receive rifaximin 400 mg 3 times daily or to neomycin 1 g 3 times daily. Both drugs were administered orally as tablets during 14 consecutive days each month, for a period of 6 months. Neuropsychiatric signs were evaluated at baseline and every 30 days until the final assessment. In all patients, a progressive and important reduction in hepatic encephalopathy grade was observed; there was no significant difference detected between the 2 groups. Both treatments reduced serum ammonia levels; however, no significant difference between the groups was found. The FDA-approved dosage of rifaximin for use with hepatic encephalopathy is 550 mg twice daily. Neomycin is FDA approved as adjunctive therapy in the treatment of hepatic encephalopathy.

rifaximin (Xifaxan) versus trimethoprim-sulfamethoxazole (Bactrim)

A total of 72 American adults with acute diarrhea traveling in Mexico were enrolled in a randomized, double-blind, clinical trial evaluating rifaximin (200, 400, or 600 mg 3 times daily) or trimethoprim/sulfamethoxazole (150/800 mg twice daily) for 5 days.¹⁰⁶ Treatment results were compared to data from 2 placebo-treated historical control populations. Duration of diarrhea was shortest in the rifaximin 200 mg 3 times daily group, although this difference was not statistically significant. Compared to historical controls, rifaximin reduced the number of unformed stools passed in the first 24 hours after treatment (3.3 versus 5.1; $p=0.008$ and $p=0.0001$). Clinical failure occurred in 11% and 29% of patients treated with rifaximin and trimethoprim/sulfamethoxazole ($p=NS$). Eradication of the enteropathogens occurred in 80% (16 of 20 patients) of rifaximin-treated group and 100% (7 of 7 patients) of the trimethoprim/sulfamethoxazole-treated group ($p=NS$). The FDA-approved dosage of rifaximin is 200 mg 3 times a day for 3 days.

tinidazole (Tindamax) and metronidazole (Flagyl)

A double-blind, randomized, trial compared the safety and efficacy of a single day split-dose of metronidazole 1.6 gm ($n=67$) to tinidazole 2 gm given as a single dose ($n=65$) for the treatment of vaginal trichomoniasis.¹⁰⁷ Patients ($n=67$) were symptomatic with the groups having similar baseline characteristics. Cure rates were 98.5% and 100% for metronidazole and tinidazole, respectively ($p=NS$). Adverse effects were mild.

META-ANALYSES

An analysis of randomized controlled trials evaluated the efficacy of antibiotic therapy for CDAD.¹⁰⁸ The analysis also aimed to identify the most effective antibiotic treatment for CDAD in adults and to determine the need for stopping the causative antibiotic during therapy. A total of 15 studies with 1,152 participants with diarrhea who recently received antibiotics for infections other than *C. difficile* were included. Definition of diarrhea varied among studies from 2 loose stools per day with associated fever or at least 6 loose stools in 36 hours. Nine different antibiotics were investigated: vancomycin, metronidazole, fusidic acid, nitazoxanide, teicoplanin (not available in the United States), rifampin, rifaximin, bacitracin, and fidaxomicin. No single antibiotic was clearly superior to the others.

Two meta-analyses evaluating the treatment of cryptosporidiosis in immunocompromised individuals were published.^{109,110} Nitazoxanide reduced the oocyst burden compared to placebo [relative risk (RR) 0.52; 95% CI, 0.3 to 0.91]. Benefits in the HIV-positive participants were not clear (RR, 0.71; 95% CI, 0.36 to 1.37).

SUMMARY

A variety of antibiotics are utilized in the treatment of gastrointestinal related infections and bacterial vaginosis.

Rifaximin (Xifaxan) has been shown to reduce the duration of loose unformed stool due to traveler's diarrhea compared to placebo. Rifaximin is not systemically absorbed and, therefore, has relatively few systemic adverse effects. Rifaximin has been shown to have similar efficacy compared to ciprofloxacin for treatment of traveler's diarrhea; the rifaximin dosage studied was higher than the FDA-approved dosage. Rifaximin was approved for use for irritable bowel syndrome with diarrhea in 2015, and current clinical guidelines recommend its use over no drug treatment. Rifaximin (Xifaxan) and neomycin are approved for hepatic encephalopathy and have been compared in only one small double-blind trial, using a rifaximin dosage studied was higher than FDA-approved dosage. Neomycin is additionally indicated for pre-operative bowel preparation.

Nitazoxanide (Alinia) is the only drug approved in this review for the treatment of cryptosporidiosis. Paromomycin, although not FDA approved, is used for treatment of cryptosporidiosis.

Tinidazole (Tindamax) and metronidazole oral are recommended by the CDC for the treatment of trichomoniasis. Tinidazole and metronidazole had similar efficacy in a single-dose study for the treatment of vaginal trichomoniasis. Tinidazole and metronidazole (Flagyl) are oral alternatives to vaginal preparations for the management of bacterial vaginosis (BV) and have similar cure rates. Tinidazole and nitazoxanide are indicated for the treatment of giardiasis. Tinidazole offers a single-dose regimen, while nitazoxanide is available as an oral suspension for this indication.

Metronidazole ER (Flagyl ER) is FDA-approved for the treatment of BV; the CDC does not include this once-daily dosage regimen in the preferred recommended treatments in the management of BV. There is very little data available comparing metronidazole ER to other BV treatments at this time.

Metronidazole, tinidazole, and paromomycin are also indicated for the treatment of intestinal amebiasis.

The 2010 Society for Healthcare Epidemiology of America (SHEA) and Infectious Diseases Society of America (IDSA) guidelines for the treatment of *C. difficile* infection in adults recommend oral metronidazole as the drug of choice for the initial episode of mild-to-moderate *C. difficile* infection. Vancomycin oral capsules (Vancocin) are FDA-approved for the treatment of CDAD and recommended as preferred oral therapy for severe *C. difficile* infection in the 2010 SHEA/IDSA guidelines. Vancomycin oral capsules are not systemically absorbed and should not be used for systemic infections. Fidaxomicin (Dificid), although not available at the time the 2010 guidelines were made public, offers a simpler treatment regimen and an alternative in the treatment of CDAD as compared to vancomycin. Fidaxomicin is dosed once daily, vancomycin is dosed 4 times a day. An update to these IDSA guidelines is projected for Spring 2016.

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